

## **2. Nontechnical Abstract**

In the United States, over 50,000 patients per year develop colon cancer that has spread to the liver. Surgery offers patients with liver spread of colon cancer a one-third chance of cure, but the majority of patients have few effective treatment options. The average time to disease progression is 6 to 9 months in these patients while overall survival is 12 to 18 months.

There have been a numerous studies over the years employing common viruses to treat cancer. Viruses most likely act by direct tumor cell killing, and through indirect effects such as stimulating the immune system. Recent advances in molecular biology have enabled researchers to engineer viruses with traits that improve both their safety and tumor killing ability.

The current trial will study the delivery of an engineered herpes virus into the artery that supplies the liver with oxygen-rich blood, where it may infect cancer nodules that have spread from the primary cancer in the colon.

NV1020, the virus used in this study, has been modified from the herpes virus that causes cold sores (called herpes simplex virus type 1 or HSV-1). HSV-1 is widespread in the human population and infections are usually mild or asymptomatic. Occasionally HSV-1 can cause systemic illness and/or brain disease, but this is usually in newborn babies or adults with poor immunity. Fortunately, HSV-1 disease can be effectively controlled generally with prescription antiviral drugs such as acyclovir or foscarnet. NV1020 has been extensively tested in animal models that mimic HSV disease in humans. These studies include tests in mice, rats and owl monkeys. Owl monkeys are extremely sensitive to HSV infection, resembling HSV infections in immunocompromised individuals.

Studies of NV1020 have shown that the virus can kill or slow the growth of multiple types of cancer. In mouse models, injections of NV1020 directly into a tumor significantly inhibited tumor growth and prolonged survival when compared to controls. NV1020 has also been shown to retard the development of liver tumors in a rat model of liver cancer.

To ensure that NV1020 would be safe if it were to migrate to the brain (the most sensitive organ for HSV disease), NV1020 was injected into the brains of mice. These studies have shown that NV1020 is at least 5000 times safer than wild type HSV-1 in the brain. Mortality has been observed in mice injected with very high doses of NV1020 either into the brain or by infusion through the portal vein (the blood vessel that supplies the liver with digestion products from the intestines). However, direct injection of high doses of NV1020 into the liver of mice only caused mild illness at the time of infection and resolved quickly. The livers appeared completely normal when observed microscopically one month later.

Toxicity has also been studied in owl monkeys injected with NV1020 through the hepatic artery, the same route to be used in the clinical trial. Monkeys did not develop clinical signs or symptoms. Although viral DNA could be detected in other organs of the body no infectious virus could be isolated. The starting dose for the proposed Phase I clinical trial is approximately 3000 times lower, on a per weight basis, than this no-effect dose in owl monkeys.

The primary objectives of the proposed clinical study are to assess the safety and tolerability of single and multiple administrations of several doses of NV1020 in patients with colorectal metastases to the liver. The secondary objectives are to assess antitumor activity, the immune reaction and shedding of NV1020.